The Menace of Urinary Tract Infections

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Urinary tract infections (UTIs) pose as an important public health problem with considerable economic burden of more than 6 million US dollars.[1] The global annual incidence is approximately 150 million cases; around 40% women and 12% men experienced atleast one symptomatic UTI in their life-time.[1] Patients with UTI are often treated empirically and the physician's choice of antibiotics typically depends on national treatment recommendations. Therefore, antibiotic resistance has become a major problem in UTI mostly due to overprescription by practitioners.[2]

The spectrum of bacteria isolated from patients with UTI worldwide has remained largely unchanged; *E.coli* followed by *Klebsiella pneumoniae* being the most prevalent micro-organisms. However, there have been significant changes in the resistance patterns of uropathogens over the past few decades.[2]

In particular, the extended-spectrum beta-lactamase-producing *E.coli* (ESBL-EC) are emerging worldwide. The ESBL-producing strains are particularly feared as they are resistant to all penicillins, cepahlosporins (including third and fourth generation agents), and aztreonam. Furthermore, they are often cross-resistant to trimethoprim/sulfamethoxazole and quinolones. This combination of properties can significantly affect the course and outcomes of infections, both in the community and in the hospital setting.[3]

Drug resistance among Gram-negative pathogens and carbapenems increases the risk of mortality. It is also a growing concern which poses a severe threat to the health.[4]

Nitrofurantoin: An Effective Therapy for UTI

Nitrofurantoin has been extensively used for more than 60 years for the treatment of uncomplicated UTIs. However, its pharmacodynamic properties are not fully explored.[4]

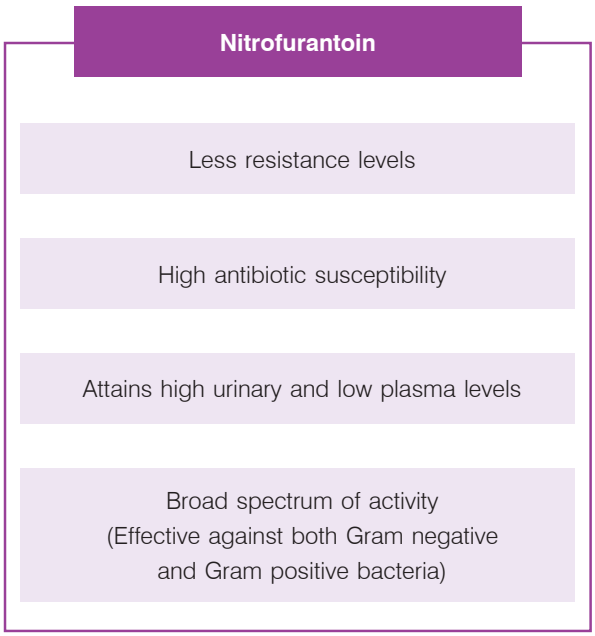
Nitrofurantoin susceptibility in bacteria correlates with the presence of bacterial nitroreductases which convert nitrofurantoin to highly reactive electrophilic intermediates. These intermediates attack bacterial ribosomal proteins, causing complete inhibition of protein synthesis, aerobic energy metabolism, DNA synthesis, RNA synthesis, and cell wall synthesis. Low concentrations of nitrofurantoin specifically inhibits inducible enzyme synthesis in bacteria. This inhibition occurs at levels equivalent to the minimum inhibitory concentration of nitrofurantoin for several bacterial species. Therefore, it can be stated that the mechanism of antimicrobial action of nitrofurantoin is unusual among antibacterials (Figure 1).[5]

The resistance rates of *E. coli* isolates for ampicillin, norfloxacin, cefuroxime are high, and therefore, their use should be discouraged in the empirical therapy.[6] According to FDA report,[7] the broad nature of this mode of action may explain the lack of acquired bacterial resistance to nitrofurantoin, as the necessary multiple and simultaneous mutations of the target macromolecules would likely be lethal to the bacteria. In a study conducted in India to assess the sensitivity pattern of *E. coli* to various drugs, the bacterial isolates were highly sensitive to nitrofurantoin (82.1%), however, the sensitivity to ampicillin, cefuroxime, ceftriaxone, norfloxacin, and ciprofloxacin varied from 11-25% only.

Pharmacokinetically, nitrofurantoin reabsorption is pH dependent and at normal urinary pH (approximately 5.5 pH); nitrofurantoin is preferentially excreted into the lower urinary tract, i.e., bladder urine, thereby increasing its potency against lower UTIs.[8]

Nitrofurantoin is bactericidal in urine at therapeutic doses. It displays urinary tract specificity, reaching high urinary levels but maintains low plasma levels.[9] According to National Institute of Health (NIH) data,[10] peak plasma concentrations following a single oral dose are usually attained at 1 to 2 hours after ingestion. Nitrofurantoin is well absorbed in the gastrointestinal tract with most absorption occurring in the

Figure 1: Nitrofurantoin: Preferred empirical drug for UTI



Adapted from:

1. Mazzariol A, Bazaj A, Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. *J Chemother.* 2017 Dec;29(sup1):2-9.
2. Picozzi SC, Casellato S, Rossini M, *et al*. Extended-spectrum beta-lactamase-positive Escherichia coli causing complicated upper urinary tract infection: Urologist should act in time. *Urol Ann.* 2014; 6(2):107-112.
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4. National Institute of Health (NIH) report on Nitrofurantoin https://toxnet.nlm.nih.gov/cgi. Accessed on March 1, 2019.
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proximal small bowel. Bioavailability is around 87% when taken on an empty stomach and increases to 94% with food. Studies have shown that therapeutic urinary concentrations of the drug are increased if nitrofurantoin is taken with food. Serum concentrations are typically undetectable, although may increase in patients with severe renal failure.[11]

Nitrofurantoin is a urinary tract antibacterial agent whose clinical effectiveness depends on the high urinary drug levels encountered during therapeutic drug dosage. Under these conditions, only low blood drug concentrations are usually found. Nitrofurantoin only achieves therapeutically active concentrations in the lower urinary tract.[11]

On the basis of urinary nitrofurantoin excretion determined after oral and intravenous drug administration, orally administered nitrofurantoin in a suitable dosage form is well absorbed.[11]

Nitrofurantoin is quickly distributed into most body fluids and is rapidly excreted in large amounts in bile and urine. With the exception of the active drug secretion in the kidney tubule and biliary drug transport, nitrofurantoin transfer across body membranes occurs by diffusion.[8]

Nitrofurantoin has a short elimination half-life in whole blood or plasma. In conjunction with its rapid excretion by the primary routes, there is little evidence for any prolonged binding of nitrofurantoin to either plasma proteins or tissues.[9]

The first-order kinetics involved in nitrofurantoin absorption and elimination is most appropriately described by a one-compartment open model. Biliary and urinary excretion of unchanged nitrofurantoin and enzymatic degradation are the primary means of elimination.[11]

Considering the broad spectrum of activity of nitrofurantoin covering virtually most uropathogens, its role as a frontline therapy of UTI stands justified.

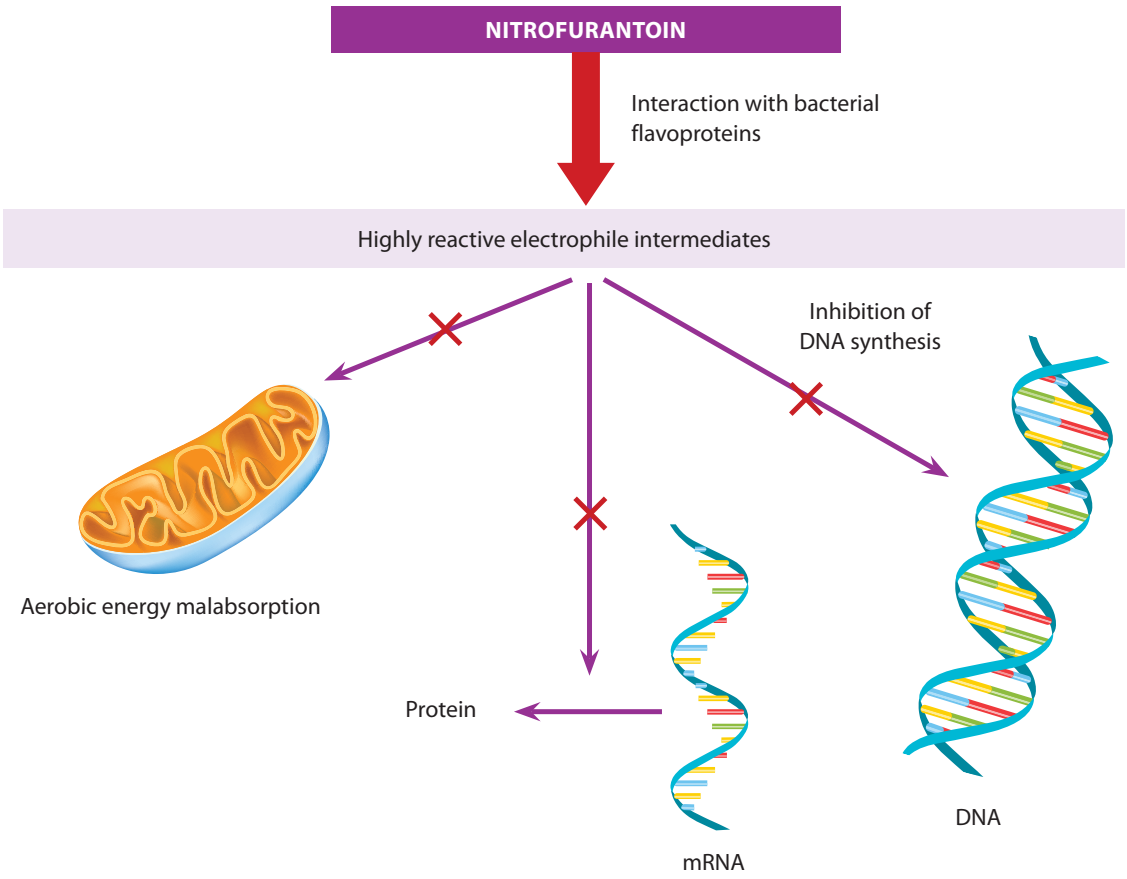
Administration

Nitrofurantoin is only available as an oral medication. It's optimal dosing remains unknown since its use was approved before modern requirements for rigorous methods for drug development. Current Infectious Disease Society of America guidelines recommend nitrofurantoin monohydrate/macrocrystals dosage to be 100 mg twice daily for 5 days for the treatment of lower urinary tract infections. A 7-day course of 100 mg twice daily is also considered acceptable. Courses of less than 5 days are shown to be less effective and are no longer recommended. Dosing for long-term prophylaxis of urinary tract infections is 50 mg to 100 mg once daily at bedtime.[12]

Tolerability

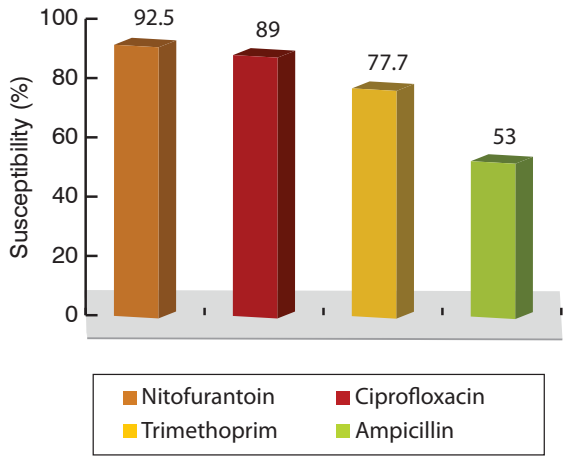
Nitrofurantoin is a relatively safe drug compared to alternatives. Comparator drugs such as trimethoprim-sulfamethoxazole and ciprofloxacin often have more reported side effects like nausea, vomiting, loss of appetite, and diarrhea. These symptoms usually develop in the first week of therapy. Modern formulations, specifically the macrocrystalline form of nitrofurantoin, have less frequency of these effects due to attempts by manufacturers to alter the crystal size, which effects gastrointestinal absorption.[12]

Figure 2: Mechanism of action of nitrofurantoin



Adapted from: Waller TA, Pantin SA, Yenior AL, Pujalte GG. Urinary Tract Infection Antibiotic Resistance in the United States. *Prim Care.* 2018 Sep 1;45(3):455-66.

Figure 3: Superior antimicrobial susceptibility of nitrofurantoin



Adapted from: National Institute of Health and Family Welfare Report http://pbhealth.gov.in/amr_guideline7001495889.pdf. Accessed on March 6, 2019.

Superiority of Nitrofurantoin Against Other Drugs for UTI

In a comparative study conducted on patients suffering with UTI, nitrofurantoin showed high cumulative probabilities of antibiotic susceptibility (92.5%) which were consistently higher than those to trimethoprim-sulfamethoxazole (77.7%), ciprofloxacin (89%) and ampicillin (53%).[8] In another trial comparing the efficacy of nitrofurantoin, trimethoprim/sulfamethoxazole, ciprofloxacin and amoxicillin, all the drugs were found to be equally effective, however, nitrofurantoin displayed less resistance potential in contrast to its comparators reinstating its role as a frontline treatment option for UTI.[9]

In a study comparing fosfomycin vs. nitrofurantoin, the latter displayed good sensitivity against ESBL-EC; the only oral antibiotic to do so.[13] Nitrofurantoin may be another alternative option for treating uncomplicated UTI caused by ESBL-EC in mainly outdoor settings or for uncomplicated UTI. Being a developing country, increasing resistance to high-end

Nitrofurantoin has been recommended as first line therapy for treatment of UTIs as per NICE and IDSA guidelines

antibiotics is adds a significant burden to health budget. However, Nitrofurantoin has proven to be cost effective in a country like India. The treatment of infections in general needs a careful approach adhering to recommended antibiotic guidelines to prevent the emergence of multidrug-resistant organisms.[4]

In another study conducted in women with uncomplicated UTI, 5-day nitrofurantoin, compared with single-dose fosfomycin, resulted in a significantly greater likelihood of clinical and microbiologic resolution at 28 days after therapy completion.

As per a clinical study, prophylaxis with 100 mg of nitrofurantoin for 9 months led to fewer women experiencing a UTI during prophylaxis and a lower mean number of UTIs per woman (0.6 episodes per woman vs 1.6 episodes per woman).Therefore, Nitrofurantoin can also be used as a step down treatment following complicated UTIs.[14]

Use of Nitrofurantoin in CKD Patients

According to Medicine and Healthcare Product Regulatory Agency Nitrofurantoin can be used in patients with an estimated glomerular filtration rate (eGFR) of not less than 45 ml/min/1.73m^2.

Infact a short course (3 to 7 days) may be used with caution in certain patients with an eGFR of 30 to 44 ml/min/1.73m^2 also to treat lower urinary tract infection with suspected or proven multidrug resistant pathogens.[15]

In a population-based study conducted in Canada on patients with low estimated glomerular filtration rate, (median 38 mL/min per 1.73 m^2), 1 of 4 antibiotics had been prescribed for urinary tract infection: nitrofurantoin, ciprofloxacin, norfloxacin or trimethoprim–sulfamethoxazole. The baseline efficacy of the 4 antibiotic groups were similar. However, in this study, it was concluded that the presence of mild or moderate reductions in estimated glomerular filtration rate did not justify avoidance of nitrofurantoin.[16]

Conclusion

Nitrofurantoin is now effectively used across various countries as the preferred drug for empirical treatment of UTIs. National Health and Family Welfare[11] and National Institute for Health and Care Excellence (NICE)[12] guidelines prefer nitrofurantoin to any other drug for the empirical treatment of UTI. Infectious Disease Society of America (IDSA) guidelines[12] also recognize the potency of nitrofurantoin as the preferred empirical therapy choice for the treatment of UTI. Thus, it can be concluded that nitrofurantoin is a preferred empirical treatment of lower UTIs.

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